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Density Functional Theory Calculations for Resveratrol

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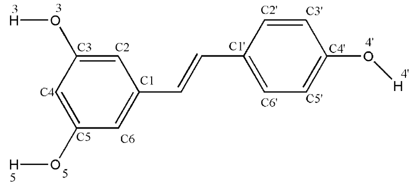
Abstract—The calculations based on the density functional theory (DFT) have been used to study the structure–activity of resveratrol in the chain reaction of autooxidation. According to the geometry obtained by using a B3LYP/6-31G**, the HOMO, LUMO of resveratrol and the spin density, the single electron distribution of the 4′- and 5-radical of resveratrol were calculated, it was found that resveratrol is a potential antioxidant. The 4′-hydroxyl group of resveratrol is more reactive than 3- and 5-positions because of the resonance effects. The dominant structure of the resveratrol radicals is a semiquinone structure which determines the stability of radicals, and the unpaired electron is mainly distributed to the O-atom and its *ortho* and *para* positions. The antioxidant activity of resveratrol is related to the spin density and the unpaired electron distribution of the O-atom.

Introduction

There is strong evidence that many of the disease of old age, notably Alzheimer's disease, Parkinsons disease, artherio-sclerosis and cancer are associated with the redundant radicals produced in vivo.[1] Recently, there has been a growing interest in selecting efficient and safety antioxidants from the natural compounds, such as flavonoids, vitamin E and other phenols.[2]



Resveratrol (3,4′, 5-trihydroxystilbene) is a naturally occurring plant phytoalexin which is synthesized by several plants in response to adverse conditions, such as environmental stress or pathogenic attack.[3] Resveratrol has been found in mulberries, peanuts and grapes.[4] Growing evidence suggests that resveratrol plays a role in the prevention of human pathological processes, such as inflammation, atherosclerosis, and carcinogenesis.[5] The antioxidant activity of resveratrol is related to its hydroxyl (OH) groups which can scavenge free radicals produced in vivo.[6,7] The experimental data demonstrate that the molecules which H-atoms of three OH groups are all replaced by CH_3 group or without the three OH groups lose their antioxidant activity.[8] When the 4′-hydrogen is substituted by CH_3, the effective dose to achieve 50% bioeffectivity (EC_{50}) value of 2,2-diphenyl-1-picrylhydrazyl radical (DPPH), which is used to express the antioxidant activity, is 48.6. Moreover, the EC_{50} value is 30.1 while the 3- or 5-hydroxyl is replaced by CH_3. Stivala used the thermodynamic parameters, the formation enthalpies (ΔH_f) calculated by semi-empirical method PM3 to discuss the antioxidant activity of the *cis*-reveratrol and *trans*-resveratrol.[8] However, in general, the PM3 method can not give the fine geometry and unpaired electron distribution of a molecule. By contrast, DFT had been proved to be reliable in the study of energetic and geometrical properties of proton transfer and other ion–molecule reactions.[9] In this work, the geometry, the spin density and the unpaired electron distribution can be obtained accurately by B3LYP/6-31G** method, and will be more helpful to elucidate the antioxidant activity mechanism of resveratrol.

Method

The original structure of the resveratrol from AM1 has been calculated by B3LYP/6-31G** method.[10–12] The

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single electron distributions were obtained by adding the keywords pop = naturalorbitals. Then, B3LYP/6-311G** was used to calculate the single point energy. All calculations were carried out with the program GAUSSIAN98W.[13]

Results and Discussion

Geometry

Since 3- and 5-positions have the same structure, only the 5-position radical was used to study in this work. The scavenging activity of phenolic antioxidant is determined by the O–H bond dissociation energy (BDE),[14] and the O–H BDE is mainly governed by the stability of the phenoxyl free radical generated after H-abstraction for the antioxidant. Generally, the factors enhancing the stability of the free radical will increase the antioxidant activity. The polar effect, including inductive and resonance stabilization, is responsible for the stability of parent molecule (SPM), and the spin delocalization of the unpaired electron determines the stability of phenoxyl radical (SPR).[15]

Figure 1 shows the optimized geometry of resveratrol and its radicals. Resveratrol (I) is a conjugated molecule in which two benzyl-rings are connected by a double-bond because all bond lengths of C–C are in the range of 1.34–1.41 Å. Although there is not significant difference between the bond length of O4′–H4′ which is 0.9663 Å and those of the O3–H3 and O5–H5 bonds which are 0.9661 Å, it indicates that the abstraction of 4′-H is easier than 3-H and 5-H. The 4′-radical has four different resonance structures (Fig. 2a–d), in which the unpaired electron shows a delocalization between the atoms 4′, 1′, 5′ and 3′. The C4′–O4′ bond is rather short at 1.2469 Å in 4′-radical (II). This length is a value near those of the double bond 1.227 Å in acetone, compared to resveratrol which is 1.3654 Å. The bond lengths of C1′–C2′, C1′–C6′, C3′–C4′ and C4′–C5′ are between 1.43–1.46 Å, and they are rather longer than that of the C2′–C3′ and C5′–C6′ which are at 1.3669 and 1.3647 Å separately. So, the dominant structure of 4′-radical is structure (b), in which the unpaired electron is disposed on whole molecule by the double bond. The 5-radical (Fig. 2a′,–d′) also have the same resonance structure as the 4′-radical, but the unpaired electron is mainly distributed on the atoms 5, 2, 4 and 6. According to the bond length values of 5-radical (Fig. 1, III), the dominant structure is (b′). The unpaired electron on the C_2 of the 5-radical can not conjugate with the double bond, on the contrary, the unpaired electron of the 4′-radical is on $C_{1'}$ so that it can conjugate with the double bond. Based on the above analysis of the resonance structure, it can be concluded that the radicals of reveratrol are stabilized by a contribution of semi-quinone resonance structure which the unpaired electron is distributed on the *ortho*- and *para*-position of the O-atom. The 4′-radical would transfer the single electron to A-ring by the resonance and the 5-radical would not have this resonance.

HOMO and LUMO

Both the highest occupied molecular orbital (HOMO) and the lowest unoccupied molecular orbital (LUMO) are the main orbitals taking part in the chemical reaction. The HOMO energy which characterizes the ability of electron-giving is appropriate to represent the free radical scavenging efficiency of phenolic compounds because the process to inhibit auto-oxidation may include the electron-transfer besides the abstraction of the H-atom.[17] The HOMO (−5.48 ev) and LUMO (−1.45 ev) are π-like orbitals (Fig. 3) and they are delocated in the whole molecule except the 3- and 5-hydroxyl. Considering the disposition of HOMO and LUMO orbitals, the HO group of 4′-position is easily attacked by either the electronphilic or necleophilic

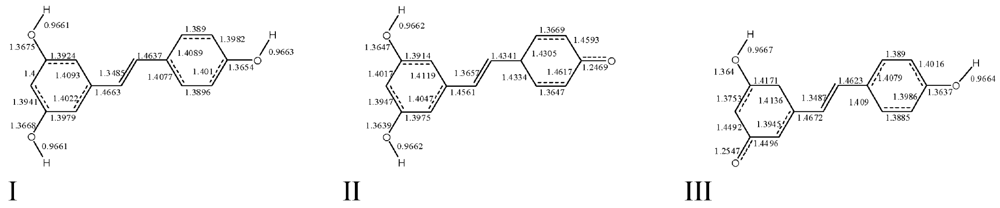
I II III

Figure 1. The geometry of resveratrol and its radicals optimized by B3LYP/6-31G** (bond-length in angstroms).

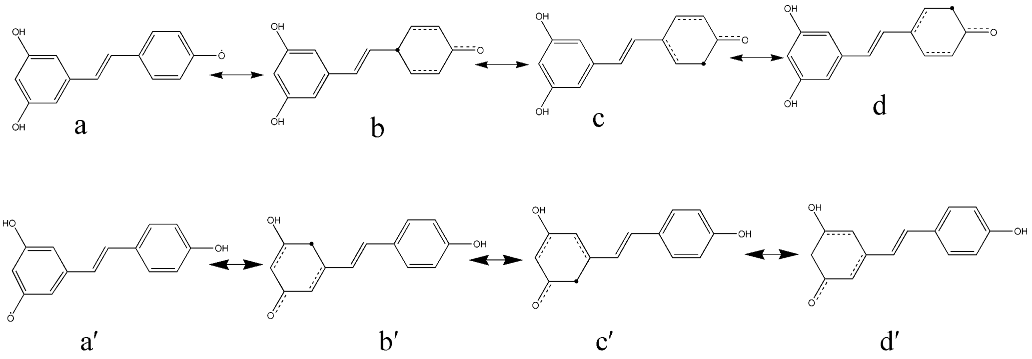
a b c d
a′ b′ c′ d′

Figure 2. The resonance structures of the radicals (a, b, c, d, 4′-radical; a′, b′, c′, d′, 5-radical).

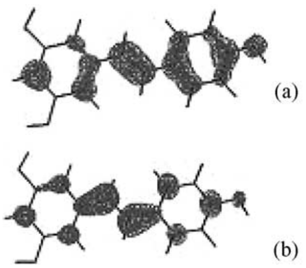

Figure 3. The density distributions of HOMO (a) and LUMO (b).

agents, such as radicals, metal ions and O_2^-. In contrast with the 4′-position, the 3- and 5-positions have little chance to react with the agents. From the D(O–H) value of 4′-position (352.1 kJ mol^{-1}) and 5-position (374.6 kJ mol^{-1}) (Table 1), the H-atom of 4′-position is more abstracted than the 5-position. The HOMO (−6.45 ev) of 4′-radical is lower than 5-radiacal (−5.72 ev) and the LUMO (−3.69 ev) is higher than 5-radical (−3.70 ev). These results imply that the 4′-radical is more stable than the 5-radical.

Spin density and unpaired electron distribution of radicals

The most important quantum property of the radicals is well given by the total spin density P_s (Fig. 4) computed at B3LYP/6-311G** level. P_s characterizes the distribution of the electron spin which decides the stability of radicals. Figure 4(a) shows that the spin density is distributed over the whole molecule, while Figure 4(b) is more concentrated on the A-ring. The spin density of the $O_{4'}$ atom is 0.31 (a) which is lower than the O_5 atom (b) at 0.42.

The natural orbital analysis which can reflect the single electron distribution was calculated by B3LYP/6-31G** method. Obviously, the distribution of the single electron (Fig. 4c and d) shows the similar distribution of the spin density. This supports the conclusion that 4′-radical is more stable than 5-radical.

Table 1. Energies of resveratrol and its radicals. D(O–H) = $E_R + E_H$-E (E, E_R, E_H denote the energies of resveratrol, radical and the hydrogen[16])

Compd		HOMO/ev	LUMO/ev	E_{total}/hatree	D(O-H)/kJ mol^{-1}
Resveratrol		−5.48	−1.45	−766.57	
4′-radical	α	−5.64	−1.86	−765.94	352.1
	β	−6.45	−3.69		
5-radical	α	−5.89	−1.83	−765.93	374.6
	β	−5.72	−3.70		

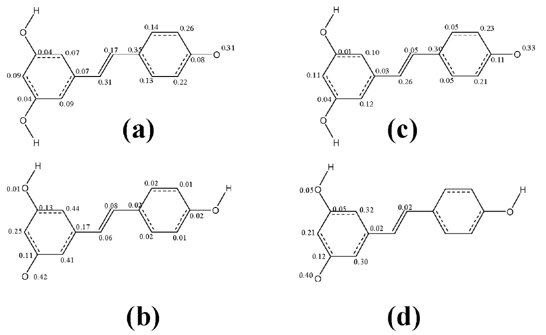

Figure 4. The total spin density of 4′-, 5-radical (a, b) and their unpaired electron distribution (c, d).

Conclusions

Our results manifest that the resveratrol is a potential antioxidant because its radicals have a semi-quinone structure in which the unpaired electron mainly is distributed on the *para* position of the O-atom. The hydroxyl groups and the double bond of resveratrol contribute to hindering the autooxidation of radicals produced in vivo. Simultaneously, the DFT method can provide a reliable geometry and a fine electron structure to explain the structure–activity relationship of resveratrol.

Acknowledgements

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